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A Phase I Study of Fludarabine, Cytarabine, and Oxaliplatin in Patients with Relapsed or Refractory Acute Myeloid Leukemia

Apostolia-Maria Tsimberidou[1], **Michael J. Keating**[2], **Elias J Jabbour**[2], **Farhad Ravandi-Kashani**[2], **Susan O'Brien**[2], **Elihu Estey**[3], **Neby Bekele**[4], **William K. Plunkett Jr.**[5], **Hagop Kantarjian**[2], and **Gautam Borthakur**[2]

[1]Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Houston, TX

[2]Department of Leukemia, Division of Cancer Medicine, the University of Texas MD Anderson Cancer Center, Houston, TX

[3]Division of Hematology, University of Washington School of Medicine, Foster City, CA

[4]Gilead sciences, Foster City, CA

[5]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX.

Abstract

Purpose—The combination of cytarabine and fludarabine was associated with superior clinical outcomes compared to high-dose cytarabine in relapse acute myeloid leukemia (AML). We conducted a phase I study combining oxaliplatin with cytarabine and fludarabine for patients with relapsed or refractory AML.

Patients and Methods—Patients had histologically confirmed disease, performance status 0-2 and adequate organ function. The regimen consisted of increasing doses of oxaliplatin (25, 30, or 35 mg/m^2/d) on days 1-4 (escalation phase) and fludarabine (30 mg/m^2) and cytarabine (500 mg/m^2) on days 2-6, every 28 days for up to 6 cycles. The dose-limiting toxicity (DLT) was defined as any symptomatic grade ≥3 non-hematological toxicity lasting ≥ 3 days and involving a major organ system.

Results—Twenty-seven patients were registered between January 2008 and November 2009. Twelve patients were treated in the dose escalation phase and 15 at the maximum tolerated dose (MTD) for oxaliplatin (30 mg/m^2; expansion phase). All patients were evaluable for toxicity and

Correspondig author: Dr. Tsimberidou, MD, PhD at the Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 455, Houston, Texas 77030, USA, or at atsimber@mdanderson.org, Tel: 713.792.4259, Fax: 713.794.4297.

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response. Only one of 27 patients received the second cycle; the remaining patients received no further study treatment owing to slow recovery from toxicities and/or physician decision. Grade 3-4 drug-related toxicities included diarrhea (grade 4) and elevated levels of bilirubin (grade 3) and aspartate transaminase (grade 3). Three patients had a complete remission and 2 patients CR without platelet recovery.

Conclusion—Oxaliplatin, cytarabine, and fludarabine had antileukemic activity in patients with poor-risk AML, but it was associated with toxicity. Different schedules and doses may be better tolerated.

Keywords

Fludarabine; Cytarabine; Oxaliplatin; AML; Therapy

Introduction

Acute myeloid leukemia (AML) is the most common type of leukemia in adults, but it continues to be associated with the lowest overall survival rate of all leukemias. Despite progress in the understanding of the pathophysiology of AML, 20-40% of patients are refractory to standard induction chemotherapy and 50-70% of patients at first complete remission [1] are expected to have relapsed AML within 3 years; the prognosis following AML relapse is dismal [2, 3]. High-dose cytarabine (Ara-C)-based therapy has been the cornerstone of salvage chemotherapy for relapsed or refractory AML. The CR rate in this clinical setting is approximately 30% [3]. The addition of other cytotoxic agents to cytarabine therapy, such as mitoxantrone or mitoxantrone combined with etoposide was associated with increased toxicity without significant improvement in CR rates [4].

Fludarabine (30 mg/m^2) and cytarabine (0.5 g/m^2/h for 2-6 h daily) administered once daily for 5 days was superior to high-dose cytarabine (3 g/m^2 over 2 h every 12 h for 2-6 days) for AML in relapse after an initial CR duration of >1 year [5].

Oxaliplatin, a third-generation platinum compound, has shown activity in patients with Richter's syndrome, relapsed/refractory chronic lymphocytic leukemia, and non-Hodgkin lymphoma [6]. Oxaliplatin is comprised of an organoplatinum complex in which the platinum atom is complexed with 1, 2 diaminocyclohexan carrier ligand and with an oxalate ligand[7, 8]. In contrast to cisplatin and carboplatin, oxaliplatin causes minimal renal or auditory toxicity [8, 9]. In our experience, the combination regimen of oxaliplatin, fludarabine, cytarabine, and rituximab had activity in patients with advanced lymphocytic leukemia, particularly in patients with large cell transformation (i.e., Richter's syndrome), with a 58% response rate [6].

Preclinical data have demonstrated the synergistic cytotoxicity of cisplatin in combination with the nucleoside analogs cytarabine [10] and fludarabine.[11, 12] In the clinic, the timed, sequential administration of fludarabine followed by cytarabine causes an increase of 40% to 200% in the cellular concentrations of the active triphosphate of cytarabine in leukemia cells [13, 14]. We hypothesized that the fludarabine-cytarabine combination would increase the sensitivity of leukemia cells to oxaliplatin by inhibiting DNA excision repair of the

oxaliplatin adducts, thereby resulting in synergistic cytotoxicity in AML. In AML, increases in DNA repair processes have been suggested as the mechanism underlying resistance to agents that form DNA adducts. However, this increased capacity for excision repair could provide an opportunity for incorporation of nucleoside analogs into the DNA repair patch. Such incorporation at once blocks DNA repair and initiates signals for cell death [15]. We hypothesized that treatment of AML with nucleoside analogs and oxaliplatin would create a mechanistic interaction of these agents that will increase the killing of leukemia cells.

We therefore, conducted an exploratory phase I study combining oxaliplatin with cytarabine and fludarabine for patients with relapsed or refractory AML. In patients with relapsed disease, enrollment was limited to patients in first relapse whose duration of first complete response [1] was < 1 year.

The primary objectives of the study were to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of oxaliplatin in combination with fludarabine and cytarabine; to assess the CR and CR with incomplete platelet recovery (CRp) rates; and to determine the safety and toxicity profile of combination therapy with oxaliplatin, fludarabine, and cytarabine in patients with relapsed or refractory AML.

The secondary objectives were to determine the duration of response, if any, and to assess toxicity in patients with relapsed or refractory AML.

Patients and Methods

Patient characteristics

Eligibility criteria were histologically or cytologically confirmed relapsed or refractory acute myeloid leukemia (AML) with prior remission < 1 year, performance status 0-2 (Zubrod scale), adequate renal and hepatic function (defined as serum creatinine ≤ 2 mg/dL and/or creatinine clearance > 40 mL/min, bilirubin ≤ 2.0 mg/dL, and aspartate transaminase (SGOT) and alanine transaminase (SGPT) < 3X the upper limit of normal for the reference laboratory value unless due to leukemia. Uncontrolled infection, intolerance to any of the agents in the regimen, pregnancy, and lactation were reasons for exclusion. Enrollment had to be at least 4 weeks after prior chemotherapy. Before enrollment, all participants gave informed consent, and the study was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board.

Treatment

In the dose-escalation phase of the study, oxaliplatin was given at escalating doses of 25 mg/m^2 (dose level 1), 30 mg/m^2 (dose level 2), and 35 mg/m^2 (dose level 3) in a 30-minute infusion on days 1 to 4 (**Table 1**). Fludarabine was given at 30 mg/m^2 intravenously on days 2 to 6, and cytarabine was administered at 500 mg/m^2 by continuous intravenous infusion on days 2 to 6. Cycles were to be repeated every 28 days. All patients received antibacterial, antiviral, and tumor lysis prophylaxis as per institutional standards. In addition, each patient received the following antiemetic regimen approximately 30 minutes prior to chemotherapy during each cycle: dexamethasone at 20 mg intravenously on days 1-4, 5-HT3 antagonist (ondansetron at 8 mg intravenously every 8 hours or granisetron at 1 mg intravenously or

dolasetron at 100 mg intravenously or by mouth), and lorazepam at 1 to 2 mg intravenously (optional).

Statistical considerations

The statistical design was based primarily on patients at first relapse with CR duration of < 1 year. This phase I study was designed using an outcome-adaptive Bayesian procedure described by Thall and Cook [16]. A family of trade-off contours derived from elicited (efficacy, toxicity) probability pairs were used to quantify the desirability of each dose for the next cohort of patients after prior probabilities were updated based on the efficacy and toxicity in the previous cohort. The program "efficacy toxicity dose finding," available on the Department of Biostatistics and Applied Mathematics website, was used to design the trial, which varies the dose of oxaliplatin. Efficacy was defined as CR and toxicity as symptomatic adverse events ≥ grade 3 that persisted for ≥ 3 days. Patients were evaluated for response and toxicity within the first cycle of treatment (1 month). The upper limit for probability of toxicity was 0.30, the lower limit for probability of efficacy was 0.40.

Three efficacy-toxicity points, (0.30, 0), (0.4, 0.3), and (1.0, 0.5), were used to establish the efficacy-toxicity contours. After entry into each cohort of at least 3 patients, the design determined whether any of the 4 doses was acceptable, i.e., whether any was plausibly (cut-off = 0.01) associated with an efficacy rate of at least 0.40 and a toxicity rate of no more than 0.30. In case more than 1 dose was acceptable, the trade-off contours were to be used to select the dose for the next cohort.

We used an additional stopping rule for monitoring safety based on Bayesian posterior probabilities. Specifically, if there is a 90% chance that posterior probability that toxicity rate at a given dose exceeds 30%, patient accrual stops at that dose. For each dose, we used independent beta distributions with parameters a=0.3 and b=0.70. The posterior probability given above was exceeded at a given dose if 3/3, 4/6, 5/9, 6/12, 8/15, 9/18, 10/21, 11/24, 12/27, 13/30, 14/33, or 15/36 toxicities were observed at a given dose.

Response was assessed using the standard response criteria. Response duration was measured from the time of response to the time of disease progression or death, whatever occurred first. Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 3.0.

The dose-limiting toxicity (DLT) was defined as any symptomatic grade 3 or higher nonhematological toxicity lasting ≥ 3 days and involving a major organ system (heart, brain, kidney, lung, and liver).

Results

Demographics

Twenty-seven patients were registered between January 2008 and November 2009: 12 patients in the dose escalation and 15 patients at the expansion phase of the study. The trial was ended early due to funding restrictions. All 27 patients received the first cycle of treatment and were evaluable for toxicity and response. Cycles were to be repeated every 28

days. However, 26 patients were unable to receive the second cycle due to slow recovery from toxicities and/or physician preference to offer a less cytotoxic therapy. One patient received the second cycle.

Pretreatment characteristics are summarized in **Table 2**. Twelve patients were treated in escalation phase and 15 in the expansion phase. The median age was 58 years (range, 6-71). Six patients were ≥ 65 years old. There were 11 men and 16 women. Prior therapies included cytarabine in combination with anthracycline or fludarabine, mitoxantrone, clofarabine, hypomethylating agentsand/or other regimens (**Table 3**). Nine (33.3%) patients had prior stem cell transplantation. One 7-year old patient with first remission duration of 54 weeks after an allogeneic transplant was enrolled as no better salvage protocol was available at the time of enrollment.

Maximum tolerated dose

Twelve patients were enrolled on protocol from 1/2008 to 11/2009. Three patients were treated at the oxaliplatin dose of 25 mg/m^2, 3 patients were treated at 30 mg/m^2, and 3 patients were treated at 35 mg/m^2, the highest tested dose. One patient, a 49-year-old female with AML and an 11q23 del who had undergone 2 prior failed chemotherapy regimens (ADE10 and clofarabine + hydrorubicin + cytarabine) and 2 allogeneic stem cell transplantations, achieved a CR in cycle 1 but died on day 10 of cycle 2 from sepsis/organ failure. At one-month follow-up of the 3 patients treated at 35 mg/m^2 oxaliplatin, 1 patient had died on day 27 from progressive disease and subarachnoid hemorrhage not attributed to oxaliplatin. The other two patients experienced no DLT. After careful review of the protocol design and patient status by the investigators and the statistician, 3 additional patients were enrolled at the same dose level (35 mg/m^2).

One month after completion of chemotherapy, 5 of the 6 patients treated at the 35 mg/m^2 oxaliplatin dose level died. Two of the 5 patients developed Grade 3 elevation of creatinine in the setting of sepsis. Therefore, the 35 mg/m^2 oxaliplatin dose level was the dose-limiting toxicity. In addition, anti-leukemic activity was noted in 1 patient who had previously failed 4 treatments, including 2 stem cell transplantations. After protocol review by the investigators, the consensus was to continue enrolling patients at the lower dose of 30 mg/m^2, with the provision of stricter monitoring of serum creatinine and creatinine clearance levels. Fifteen additional patients were enrolled at this dose level.

Toxicity

Toxicity was summarized in **Table 3**. Grade 3-4 drug-related toxicities were mostly associated with the gastrointestinal tract and included Grade 3 increase in ALT (dose level 3, 1 patient); Grade 3-4 increase in AST (dose level 3, 1 patient; expansion phase 3 patients), Grade 3 increase in creatinine (dose level 3, 2 patients); Grade 3 increase in amylase/lipase (level 3, 1 patient; expansion phase 3 patients). Grade 3 diarrhea was noted in 1 patient in dose level 3 and in 4 patients in the expansion phase. Infections were noted in all dose levels. No additional renal toxicities were encountered in the dose expansion phase. Three of the patients treated at the dose expansion level were taken off-study prior to day 28; one due to fungemia and two due to disease progression.

Response

Five patients (3 CR and 2 CRp) responded; 1 at dose level 1, 1 at dose level 3 and others at dose level 2. Two of these 5 patients had prior allogeneic SCT. Three of the responders had diploid cytogenetics while 2 had complex cytogenetics(**Table 4**). One patient in CR and another patient with acellular marrow after treatment received allogeneic SCT.

Discussion

Despite the lack of randomized trials, salvage regimens based on the fludarabine and cytarabine combination have become a mainstay in AML therapy. On the basis of the concept of intracellular ara-CTP modulation, alternative nucleoside analogs (e.g., clofarabine, cladribine, etc.), with or without anthracyclines, have been used in place of fludarabine [17-19] [20]. While first salvage attempts using such regimens have resulted in remission rates of ≈30-60% in small studies among patients with AML, the response rates in the context of subsequent salvage have been dismal [20-23]. Among patients with AML at first salvage, the response rates depend largely on the duration of first remission, and response is poor among patients with first remissions shorter than 6 months [22].

The current study demonstrated that the maximum tolerated dose of fludarabine, cytarabine, and oxaliplatin was oxaliplatin 30 mg/m^2 on days 1-4, fludarabine 30 mg/m^2 on days 2-6, and cytarabine 500 mg/m^2 on days 2-6. The study population included in our trial represents patients with poor prognosis, as only 6 of 27 patients were receiving the study drug combination as first salvage and 75% of the patients had a first-remission duration of <6 months. In that context, remission in 5 of 27 patients in our phase I combination study of fludarabine, oxaliplatin, and cytarabine is encouraging.

Oxaliplatin remains an agent that has been investigated very little in AML, although it has demonstrated efficacy in combination with fludarabine in aggressive chronic lymphocytic leukemia. The synergistic effect of oxaliplatin and fludarabine in the killing of chronic lymphocytic leukemia cells depends on the presence of the 5′ nuclear excision repair endonuclease XPF. Activation of nuclear excision repair after oxaliplatin exposure allows fludarabine incorporation into the DNA, and the synergy of oxaliplatin and fludarabine is lost in cells lacking XPF [24]. This characteristic may allow us to preselect patients for this combination strategy. The fludarabine and oxaliplatin combination induces apoptosis by both intrinsic and extrinsic pathways, and it will be interesting to see if this combination has synergy with inhibitors of the Bcl family of anti-apoptotic proteins that are being developed clinically. Such synergy may also allow us to use lower doses of chemotherapeutic agents compared to the doses used in the current report and thus abrogate toxicity.

At the oxaliplatin dose level of 35 mg/m^2, several patients died after the DLT-defining period of 4 weeks, mostly of sepsis and multi-organ failure. Transient grade 3 elevation of creatinine was also encountered in 2 of 6 patients at this dose level. After discussion among the co-investigators and the statistician, the dose of 30 mg/m^2 was declared the MTD for accrual to the expansion phase of the study. The fact that significant infectious complications were encountered in 25 of 27 patients remains worrisome but is not unusual in such a cohort of heavily pre-treated patients with refractory/relapsed AML. Delivery of

treatment beyond cycle 1 has been difficult in this study, mostly due to slow resolution of gastro-intestinal toxicities. Based on our experience with oxaliplatin, cytarabine, fludarabine and rituximab in lymphoid malignancies, reduction in the number of days of oxaliplatin to 3 days and fludarabine and cytarabine to 3-4 days may result in a better tolerated regimen allowing for repeated administration.

In conclusion, the combination of fludarabine, cytarabine, and oxaliplatin is active in relapsed/refractory AML. Further refining of the dosing schedule and toxicity profile will allow this regimen to be investigated as a salvage therapy option in the early salvage setting and be compared to regimens currently used for AML salvage.

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Table 1

Distribution of patients, treatment cycles, and dose-limiting toxicities across tested dose levels

Oxaliplatin dose*, mg/m^2 (Days, 1-4)	Number of patients	Number of patients who completed cycle 1	Number of patients with DLT	Description of DLT**
25	3	3	0	
30	18	15	0	
35	6	4	3	Grade 3 elevation of ALT/AST T Grade 3 creatinine; renal insufficiency Grade 3 bilirubin; hyperbilirubilemia

Abbreviations: DLT = dose-limiting toxicity, ALT= alanine transaminase, AST= aspartate transaminase

*Fludarabine was given at 30 mg/m^2 intravenously on days 2 to 6, and cytarabine was administered at 500 mg/m^2 by continuous intravenous infusion on days 2 to 6. Cycles were to be repeated every 28 days.

**Dose-limiting toxicity was defined as any symptomatic ≥ grade 3 non-hematological toxicity lasting ≥ 3 days and involving a major organ system (brain, heart, kidney, liver, or lung) in the NCI Version 3.0 toxicity scale.

Table 2

Patient Characteristics

N= 27		
Characteristic	**N**	**%**
Age years, range (median)	6-71 (59)	
Age ≥ 65 yrs	6	22
Male/Female	11/16	41/59
Zubrod performance status		
0	6	22
1	16	59
2	5	19
Cytogenetic group		
Diploid	6	22
Complex	18	67
Not available	3	11
Prior MDS	5	19
Prior stem cell transplantation	9	33
Laboratory tests	**Median**	**Range**
White blood cells ($\times 10^9$/L)	4.2	0.4, 61.3
Hemoglobin (g/dL)	9.3	7.9, 11.7
Platelets (K/UL)	18	6, 118
Peripheral blood blasts (%)	62	2, 96
Bone marrow blasts (%)	56	
Bilirubin (mg/dL)	0.3	0.2, 1
Creatinine (mg/dL)	0.8	0.4, 1.3

Abbreviations: MDS= myelodysplastic syndrome

Table 3

Cycle 1 Toxicity in 27 patients treated with oxaliplatin, cytarabine, and fludarabine

Toxicity	Dose escalation phase			Expansion phase
	Level 1	Level 2	Level 3	
	n=3	n=3	n=6	n=15
Bilirubin	G4 (n=1)	G3 (n=1)	G2 (n=1) G3 (n=3) G1 (n=1)	G1 (n=2) G2 (n=3) G3 (n=2)
ALT	G1 (n=1)	G1 (n=2)	G1 (n=1) G2 (n=1) G3 (n=1)	G1 (n=6) G2 (n=3)
AST	G1 (n=1) G2 (n=1)	G1 (n=1)	G1 (n=1) G2 (n=1) G3 (n=1)	G1 (n=3) G2 (n=1) G3 (n=2) G4 (n=1)
Creatinine	G1 (n=1)	G2 (n=1)	G3 (n=2)	G2 (n=2)
Amylase	G1 (n=1)			G3 (n=3)
Lipase	G2 (n=1)		G3 (n=1)	G3 (n=3)
Diarrhea		G1 (n=1)	G2 (n=3) G3 (n=1)	G1 (n=1) G3 (n=4)
Nausea		G1 (n=1)	G1 (n=2) G2 (n=1)	G1 (n=5) G2 (n=1)
Vomiting			G1 (n=2) G2 (n=1)	G1 (n=3) G2 (n=1)
Rash			G1 (n=1)	
Infections	n=3	n=3	n=6	n=13

Table 4

Characteristics of responders to fludarabine, cytarabine and oxaliplatin

Age/Sex	PS	Dose level mg/m^2	CG	Prior therapies	First Remission Duration (weeks)	Prior SCT	Response	Survival status	Survival (days)	Cause of death
49/F	0	35	Complex	Daunorubicin, Ara-C, and etoposide, clofarabine and 2 SCT	48	Yes	CRp	Dead	80	Sepsis/organ failure
7/F	1	30	Complex	SCT	54	Yes	CR	Dead	305	Unknown
39/F	1	30	Diploid	Idarubicine, Ara-C, and sorafenib; methotrexate, epirubicin, and cisplatin	18	No	CR	Dead	181	Multi-organ failure
53/F	1	30	Diploid	Cytarabine and daunorubicin; mitoxantrone	17	No	CRp	Dead	71	Fungal septicemia
58/F	1	25	Diploid	Idarubicine and Ara-C; clofarabine, idarubicin, Ara-C, and maintenance SCT	37	Yes	CR	Alive	186+	N/A

Abbreviations: Ara-C: cytarabine; CG: cytogenetics; N/A: results not available; PS: performance status; SCT: stem cell transplant